Clinical trials suggest first-ever safe and effective treatment to prevent multidrug-resistant TB in children and adults

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Two landmark clinical trials reported at the Union Conference in Paris showed that an oral antibiotic taken for six months once-daily

substantially reduced the risk of developing drug-resistant TB.

The antibiotic levofloxacin safely reduced the risk of multidrug-resistant (MDR) tuberculosis (TB) disease in children by 56%, researchers from the Desmond Tutu TB Center at Stellenbosch University announced at the Union Conference in Paris today. The trial also showed that levofloxacin given once daily to children over 6 months, was extremely safe.

A second study, the VQUIN Trial, was presented at the same session. The VQUIN trial was conducted primarily among adults and adolescents, and found that levofloxacin reduced the risk of MDR-TB in adults and adolescents by 45%. Together, the two studies demonstrated that levofloxacin can stop the risk of MDR-TB among family and other household members, curtailing the global impact of this dangerous pathogen.

Evidence to date has been limited about MDR-TB preventive treatment since no randomized controlled trials had ever been conducted. TB-CHAMP took place in South Africa, in six research sites in five provinces serving communities with high burdens of TB and MDR-TB, focusing mainly on children below 5 years of age.

"There have been many advancements in the science around preventing drug-susceptible TB, but very little rigorous data on preventing drug-resistant TB," said Professor Anneke Hesseling, Director of the Desmond Tutu TB Center and the overall Principal Investigator of the TB-CHAMP trial, at Stellenbosch University.

"We have now found a way to safely protect children when an adult in the household has MDR-TB. The importance of safeguarding our children from drug-resistant disease cannot be underestimated. The benefit to children, their families and communities may be substantial."

"MDR-TB is one of the toughest diseases to cure, and children have always been the most neglected patients," said Professor James Seddon, co-Principal Investigator from TB-CHAMP from Stellenbosch University.

"In finding a new way to keep children safe when MDR-TB afflicts a family member, we help the whole family recover that much faster from the trauma that the disease inflicts—not just from a health perspective, but from economic and mental health perspectives as well."

"Over 450,000 people develop multidrug-resistant TB each year. Drug-resistant TB can be devastating for patients and their families," said Professor Greg Fox, Principal Investigator on the VQUIN trial, from The Woolcock Institute of Medical Research and The University of Sydney.

"We now have evidence that people with early infection can be protected from becoming sick due to drug-resistant TB. This six-month once-daily treatment can protect adults, children and adolescents and young kids from the physical, social and financial consequences of drug-resistant TB."

"Research to prevent and treat tuberculosis in children has been treated as an afterthought for far too long," said Dr. Philippe Duneton, Executive Director of Unitaid, the largest multilateral funder of TB research and development globally.

"Unitaid is pleased to be a part of efforts to elevate children's needs. This first of its kind evidence into the prevention of drug-resistant TB in children is a major advance that has the potential to protect millions of children from a debilitating illness."

In the TB-CHAMP trial, 453 children who had been exposed to an adult

with MDR-TB in their household were given levofloxacin and only five developed MDR-TB. There were very few side events from the medicine. Specifically joint pain and tendonitis, traditionally a concern, were very uncommon in children receiving levofloxacin.

In the VQUIN trial, 2,041 adults and children living with a person with MDR-TB in the household were given six months of levofloxacin and followed up for 30 months. The study took place in 10 provinces across Vietnam. It found that there were 45% fewer cases of TB in the group given levofloxacin compared to the placebo group. A lower number of cases of TB occurred in the placebo group than expected. Overall, levofloxacin was found to be safe and well-tolerated in adults and children.

TB remains one of the top causes of death in children globally and is a one of the top killers of children below 5 years of age. An estimated 30 000 children below 15 years of age develop MDR-TB disease each year, which is complex to treat with current medications, which have many side effects. The cost of treatment is high to families and to health services.

Fewer than 20% of children with MDR-TB are currently diagnosed and treated globally. This makes them one of the most neglected populations affected by TB globally. Many of these children were in close contact with an infectious MDR-TB patient and identifying these children, screening them for TB and offering preventive treatment will be critical to find more cases and also to prevent MDR-TB in children.

In December 2023, an advisory committee of the World Health Organization will consider new guidelines for MDR-TB preventive treatment. The data from the TB-CHAMP and the VQUIN trials is being shared to inform how these deliberations produce new recommendations for children and adolescents. The TB-CHAMP and VQUIN trials also

completed work on other important considerations such as acceptability of the drug regimen, feasibility, health economics, pharmacokinetics and antimicrobial resistance.

The teams from the TB-CHAMP and VQUIN trials collaborated early on, before the trials were unblinded, and combined their data on efficacy and safety in traditional and novel Bayesian approaches. Jointly, they showed that across both trials, levofloxacin reduced the risk of developing TB by 60%. Novel Bayesian analysis showed similar results for each trial, individually.

"This novel Bayesian analysis, combining data from trials in two trial populations using novel methodology developed at MRC CTU at UCL, may pave the way for combining future pediatric and adult trial data, ensuring that children are not left behind," said Trinh Duong, TB-CHAMP trial statistician and lead for the combined analyses from MRC Clinical Trials Unit at UCL.

"By carefully planning this work in advance, we have been able to present these important findings alongside the main results of the two trials, with greater potential impact on global guidelines and policy."

Provided by Stellenbosch University South Africa

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